REMARKS/ARGUMENTS

By the current amendment, claims 1, 4, and 6-12 are amended. Claims 2, 3, 5, and 13-29 are canceled. Claims 30-38 have been added. No new matter has been added.

The drawings were objected to under 37 CFR 1.83(a) because Figure 1 was alleged to fail to show details as described in the specification. The contrast setting for Figure 1 was alleged to be too high. Corrected drawing sheets in compliance with 37 CFR 1.121 (d) are provided in reply to the Office action (See Appendix A).

Claims 1, 4 and 6-12 were objected to because the recitation of "FGFR3" was not in parenthesis and did not follow the phrase it abbreviates when used for the first time in a claim. By the current amendment, this has been corrected.

Claim 1 (4 and 6-12 dependent therefrom) is objected to because the recitation of the phrase, "and normal references values in samples from subjects without bladder transitional cell carcinoma", can be substantially improved with respect to grammar. In accordance with the Examiner's suggestion, the verb "are" has been added to the noted phrase.

Claims 4 and 6-12 were objected to because the recitation of "Method according to ..." was alleged to be capable of improvement with respect to form. In accordance with the Examiner's suggestion, the phrase has been amended to read -- The method according to...--.

Claim 4 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Regarding claim 4, the Examiner argued that the word "preferably" renders the claim indefinite because it is unclear whether the limitations following the word are part of the claimed invention. The word "preferably" has been omitted by this amendment.

Claims 1, 4 and 6-12 were rejected under 35 U.S.C. 11 2, first paragraph, as failing to comply with the enablement requirement. The Examiner admits that the specification is enabling for an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or to monitor the effect of the therapy administered to the individual with this cancer. The Examiner, however, appears to argue that the specification is not enabling *to determine the stage or severity of this cancer in an individual.* Claim 1 has been amended to delete the phrase "to determine the stage or severity of this cancer in an individual." Therefore, this rejection is moot with regard to claim 1 and its dependent claims.

However, the Applicant respectfully disagrees with the Examiner's position that assessing the stage or severity of bladder transitional cell carcinoma (TCC) in an individual, as recited in new claim 30, is not enabled. As noted on page 42 of the attached article by Masood et al. (International Urology and Nephrology 36: 41-44, 2004), "High-grade transitional cell carcinoma (TCC) with lamina propria invasion (T1G3) has been shown to have a greater potential for disease progression than other superficial lesions." See Appendix B. In general, within stage T1, G3 tumors have a very poor prognosis, while G1 tumors have a good prognosis. According to the current application, 100% of G1 tumors express FGFR3, while only 59% of G3 tumors express FGFR3. See Table 5. Thus, a person of ordinary skill in the art would understand that a stage T1 tumor that does not express FGFR3 is a G3 tumor having a poor prognosis. Similarly, 49.2% of invasive stage T2 tumors

express FGFR3, while 70% of superficial stage T1 and/or Ta tumors express FGFR3. A person of ordinary skill in the art would understand that this distinction can be used to asses the likelihood that a particular tumor is invasive. In the Applicant's opinion, the expression of FGFR3 is a useful tool, in combination with other clinical parameters for evaluating the stage or severity of bladder cancer.

Claims 1,4, and 6-12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sturla et al. (British Journal of Cancer (2003) 89, 1276-1284). The Examiner argues that Sturla shows that FGFRIII3S protein, a varient of FGFR3, is expressed at very high levels in bladder cell cancer line RT112. See FIG. 3, lane h.

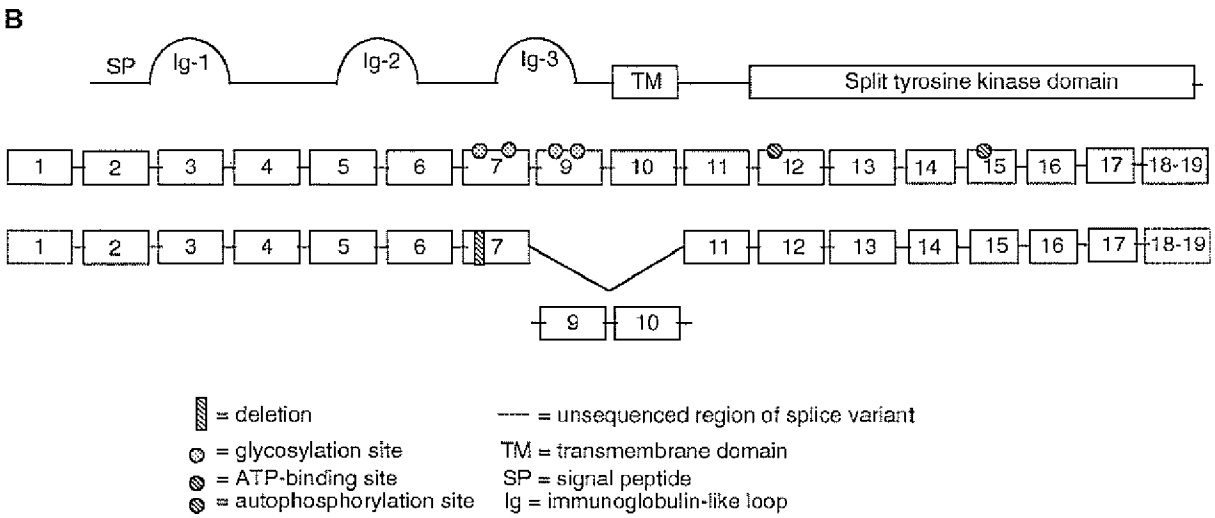
The Examiner further argues that Sturla teaches an in vitro method to detect FGFR3IIIS protein in a tumor cell line, and the comparison of the amount of FGFR3IIIS protein in a tumor cell line with reference samples. The Examiner admits that the reference Sturla does not teach direct comparison of FGFR3 levels in bladder cancer tissues vs. normal tissues.

The Examiner argues that it would have been obvious to detect bladder transitional cell carcinoma by detecting FGFR3, since Sturla teaches that FGFRIII3S protein, a varient of FGFR3, is expressed at very high levels in bladder cell cancer line RT112. The Examiner argues that the specification does not define the term "FGFR3", and therefore, it has been interpreted to include any naturally occurring FGFR3 mutants and splice variants.

The Applicant respectfully disagrees with the Examiner. It would not have been obvious to detect bladder transitional cell carcinoma by detecting FGFR3

based on the disclosure of Sturla. Sturla monitored FGFR3IIIS levels in 19 cell lines and 30 tumors. None of the tumors were bladder cancers; only two of the cell lines were derived from bladder cancers. Of these two bladder cancers, one (RT112) showed FGFRIII3S at very high levels; the other (EJ) showed *no detectable FGFR3IIIS*. See Sturla, Fig. 3, lanes (h) and (n). This would suggest to a person of ordinary skill in the art that the presence or absence of FGFR3IIIS is *not* a reliable method to detect bladder cancer, particularly since FGFR3IIIS was very common in tumor cell lines, being detected in a total of 15 of 19 cell lines. See Sturla, page 1280, Col. 1.

Additionally, the Examiner argues that FGFR3 is not defined in the specification, and therefore can include any naturally occuring mutants or variants. However, the specification clearly indicates that FGFR3 is one of four well-characterized Fibroblast Growth Factor Receptors, and is also referred to as Cek2. See page 4 of the current application. Sturla clearly states that FGFR3IIIS is a *novel variant* which is *distinct from the normal forms of the FGFR3 protein*, FGFR3IIIc and FGFR3IIIb. See Sturla, pages 1276-1277. Further, we note that the online database UniProt (http://www.uniprot.org/uniprot/P22607) specifically states that FGFR3IIIc is the canonical sequence of FGFR3. See Appendix B. Sturla teaches that FGFR3IIIS differs from the canonical sequence FGFR3IIIc in that there is "a 336 bp deletion resulting in loss of exons 9 and 10, and a 30 bp deletion in exon 7." See Sturla, page 1277, Col. 1. Additionally, Sturla includes a Figure illustrating the distinctions between FGFR3IIIc, the canonical sequence of FGFR3, and FGFR3IIIS, as shown below:



According to Sturla, sequence analysis of FGFR3111S demonstrated loss of exons 9 (encoding the second half of the third Ig-like domain) and 10 (coding for the transmembrane domain) and a 30 bp deletion in exon 7 (within the region between the second and third Ig-like loops, including a potential glycosylation site). Loss of a transmembrane domain, a glycosylation site, and portions of an Ig-like domain would be expected to significantly alter the functionality of the protein.

Thus, the FGFR3IIIS protein has significant deletions that affect structure and function. According to UniProt, only one of the three main isoforms of FGFR3 has a significant deletion, and this isoform, Isoform 3, has *only one* deletion. Thus, a person of ordinary skill in the art would not understand the term FGFR3 to include FGFR3IIIS.

Further, Sturla was published on 30 September 2003, while the earliest priority date of the current application, as admitted by the Examiner, is March 26, 2003. Therefore, Sturla is not available as prior art against the current application. We attach an abstract giving the correct publication date. See Exhibit B.

While we believe that the instant amendment places the application in condition for allowance, should the Examiner have any further comments or suggestions, it is respectfully requested that the Examiner telephone the undersigned attorney in order to expeditiously resolve any outstanding issues.

In the event that the fees submitted prove to be insufficient in connection with the filing of this paper, please charge our Deposit Account Number 50-0578 and please credit any excess fees to such Deposit Account.

Respectfully submitted,
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Appendix A